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Statistical analysis plan

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Statistical analysis plan

Does disease perception influence functional outcome among patients with low back pain? A prospective cohort study with 52 weeks follow-up

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1. Overview of analyses

This document contains the statistical analysis plan for ‘Does disease perception influence functional outcome among patients with low back pain? A prospective cohort study with 52 weeks follow-up’. The aim is to clarify analyses and to avoid misleading inference from post-hoc analyses. Therefore the statistical analysis plan has been completed prior to the availability of any outcome data. This document describes the analyses to be performed in the main study paper.

Regarding time-lines for analyses the main time points are: baseline (7 days prior to Spine Centre consultation) and follow-up (52 weeks after completion of the baseline questionnaire).

Recruitment of patients began in April 2017 and is expected to continue until February 2018. The primary analysis of the study will be conducted when the last patient enrolled has been followed for 1 year, expected in February 2019.

2. Background of the trial

The principal research question is whether ‘Believing ‘staying active is beneficial despite having low back pain’ is associated to better functional outcome after 1 year?

This study is registered at ClinicalTrials.gov (registration number: NCT03058315). The study is conducted at Silkeborg Spine Center, Denmark. Reporting follows the STROBE guidelines for observational studies in epidemiology.

2.1. Eligibility

2.1.1. Inclusion criteria.

To be eligible for the study, subjects must fulfill the following criteria:

1. Completion of the electronic questionnaire routinely delivered 7 days prior to Spine Centre consultation.
2. ≥ 18 years of age at the time of completion of the baseline questionnaire.
3. Low back pain is the primary cause of the referral to the Spine Center (not neck pain).

2.1.2. Exclusion criteria

To be eligible for this study, subjects must not meet any of the following criteria:

1. Known spinal fractures.
2. The low back pain is suspected to be caused by malignancy.
3. Unwillingness to participate.

3. Consent

Written and signed informed consent is taken from all participants prior to inclusion in the study. All patients receive usual care. Consent involves accepting data from a routinely administered questionnaire to be used for research, filling in additional questions at baseline, and filling in a questionnaire after 52 weeks.

4. Explanatory variables

Tables of summary statistics will be produced by group (agree or not to 'if pain is increasing they should stop with their physical activities'). The table will include:

Table 1. Baseline characteristics	Included In table 1	Explanatory variable	Possible confounder	Presented as	Test for Baseline differences
Age, years	√	-	√	Mean (sd)	The two-sample t-test
Female	√	-	√	Yes/no	Fisher's Exact Test
College level education	√	-	√	Yes/no	Fisher's Exact Test
Employed	√	-	-	Yes/no	Fisher's Exact Test
Sick leave, days	√	-	-	Median (iq)	The Mann–Whitney U-test
Current smoker	√	-	-	Yes/no	Fisher's Exact Test
Alcohol consumption (men > 2 daily units) (women > 1 daily unit)	√	-	-	Yes/no	Fisher's Exact Test
History of low back surgery	√	-	-	Yes/no	Fisher's Exact Test
Co-morbidity (self-reported)	√	-	-	Yes/no	Fisher's Exact Test
Health related quality of life (0-1)	√	-	-	Median (iq)	The Mann–Whitney U-test
Roland Morris Disability Questionnaire (0-23 points, high score=high disability)	√	-	-	Mean (sd)	The two-sample t-test
Chronic pain (> 12 weeks = yes)	√	√	-	Yes/no	Fisher's Exact Test
Numerical Pain Rating (0-10)	√	√	-	Mean (sd)	The two-sample t-test
STarT Back Tool (High risk)	√	√	-	Yes/no	Fisher's Exact Test
'if pain is increasing, it is a warning signal to stop with my physical activities until pain is decreasing' (0-10)	√	√	-	0-5=disagree, 6-10=agree	Fisher's Exact Test
'I think that finding the cause of pain is important for my recovery' (0-10)	√	√	-	0-5=disagree, 6-10=agree	Fisher's Exact Test
'I think X-rays and MR-scans are important part for my recovery' (0-10)	√	√	-	0-5=disagree, 6-10=agree	Fisher's Exact Test
'Have you been advised by your general practitioner to stay active despite your back pain?'	√	√	-	Yes/no	Fisher's Exact Test
'Have you been advised from a physiotherapist or chiropractor to stay active despite your back pain?'	√	√	-	Yes/no	Fisher's Exact Test

Note: The number of missing observations for each variable will be reported.

4.1. Primary explanatory variable

The main explanatory variable is associated to the statement "if pain is increasing, it is a warning signal to stop with my physical activities until pain is decreasing". The patients will be asked to rate their agreement with the statement by choosing between 11 boxes displayed on a horizontal line (0-10 Points, higher score indicating higher agreement). The scores will be labelled to the left at 0 (Do not agree) and to the right side as 10 (totally agree). Patients scoring 0-5 regarding agreement will be as coded 0 (disagreement) and patients scoring 6-10 will be coded as 1 (agreement) in all analyses.

4.2. Secondary explanatory variables

Secondary explanatory variables are: 1) 'I think that finding the cause of pain is important for my recovery' (0-10, 0-5=disagree and 6-10=agree), 2) 'I think X-rays and MR-scans are important part for my recovery' (0-100-5=disagree and 6-10=agree), 3) 'Have you been advised by your general practitioner to stay active despite your back pain?(yes/no)', 4) 'Have you been advised from a physiotherapist or chiropractor to stay active despite your back pain?(yes/no)', 5) Pain duration, 6) Numerical pain rating (0-10, continuous, normally distributed), and 7) the STarT Back Tool (high-risk/not high-risk).

If baseline pain cannot be considered normally distributed, it will be categorized as low/high using > 5 as a cut-off and tested with Fisher's Exact Test.

4.3. Baseline variables which are considered possible confounders

Age (continuous, defined as: date of baseline questionnaire completion – date of birth), gender (male or female), and college level of education (college completed: yes/no).

4.4. Other baseline variables

Other baseline variables are included with the purpose to describe the study population: Health related quality of life (EQ-5D-3L, continuous between 0 and 1), Chronic pain (pain for a 12 weeks, yes/no), employment status (working/not working), sick-leave (duration of current episode, number of days), smoker (yes/no), alcohol consumption (yes/no defined as over two units a day for men and over one unit a day for women), previous back surgery (yes/no), co-morbidity (yes/no), and the baseline Roland Morris Disability Questionnaire (RMDQ), Patrick version (0-23 points). If baseline RMDQ cannot be considered normally distributed, it will be presented with median (iq) and tested with the Mann-Whitney U-test.

5. Sample size

It is expected that approximately 33 % of patients will reply “yes” to the question “if pain is increasing they should stop with their physical activities” and 67 % will reply “no”.

Among patients replying ‘yes’, 50 % are expected to receive a clinically relevant improvement in the RMDQ score. Among patients replying ‘no’, 70 % are expected to receive a clinically relevant improvement in the RMDQ score of 30 %.

With full follow-up, group sizes (1/2), alpha 0.01, and a power of 0.9; 423 patients are needed in the analysis. To account for another distribution of group sizes and possible loss to follow-up after 52 weeks we plan to recruit 800 patients.

6. Study end

Completion of the study and submission is expected in May 2019.

We will continue recruitment until we reach 800 participants. Since consent is delivered electronically by the patients, it might not be possible to stop at exactly 800 participants. When we reach 800, the invitation to participate will be removed from the on-line questionnaire. Therefore, the actual recruited number may be between 800 and 810.

7. Statistical plan for the main outcome paper

Results with p-values < 0.01 will be considered statistically significant. Statistical analyses will be performed in Stata (IC version 14.0).

7.1. Flow chart

A detailed flow chart with reasons for exclusions and total numbers of patients in each group (agree or not agree that ‘if pain is increasing they should stop with their physical activities’) will be reported in a Figure. We will include follow-up after 52 weeks with explicit reporting of number of patients with missing outcome.

7.2. Baseline descriptions

Differences between groups will be tested using Fisher's Exact Test for categorical variables, and the two-sample t-test, or the Mann–Whitney U-test for continuous variables (Table 1). The number of missing observations will be reported.

7.3. Primary outcome analyses

7.3.1. Adjusted analysis of the primary outcome

We will compare the two groups (agree or not agree) to 'I think that finding the cause of pain is important for my recovery'. The primary outcome is the proportion of patients receiving a clinically relevant improvement in the RMDQ score defined as a 30%-improvement¹ between baseline and 52 weeks follow-up. We will apply logistic regression to estimate odds ratios. In the primary analysis we will adjust for age, gender, and educational level (Table 2). The model fit will be assessed by looking at Pearsons residuals. If the model does not fit regarding age, age will be categorized as low/high using ≥ 65 years as a cut-off in the adjusted analyses.

7.3.2. Unadjusted analysis of the primary outcome

Using the model above (7.3.1.) without including possible confounder, we will make a secondary analysis of the primary outcome (Table 2).

7.4. Secondary outcome analyses

As secondary analyses we will study the association between the secondary explanatory variables and improvement in the RMDQ score after 52. We will apply logistic regression to estimate odds ratios. The result will be presented unadjusted and adjusted for age, gender, and educational level (Table 2).

Table 2. Predictors of outcome	Numbers (%)	Adjusted Improvement RMDQ $\geq 30\%$ Odds ratio (99% CI)	Unadjusted Improvement RMDQ $\geq 30\%$ Odds ratio (99% CI)
'Pain is a warning signal to stop physical activity' (6-10, agree)			
'I think that finding the cause of pain is important for my recovery' (6-10, agree)			
'I think X-rays and MR-scans are important part for my recovery' (6-10, agree)			
'I have been advised by a general practitioner to stay active despite your back pain?' (yes)			
'I have been advised from a physiotherapist or chiropractor to stay active despite your back pain?' (yes)			
Chronic pain (duration >12 weeks, yes)			
High pain (Numerical pain rating (6-10, yes)			
High risk STarT Back Tool group (yes)			

NOTE: Results are adjusted for age, gender, and educational level. The number of missing observations for each variable will be reported.

¹ Jordan K, Dunn KM, Lewis M, Croft P. A minimal clinically important difference was derived for the Roland-Morris Disability Questionnaire for low back pain. J Clin Epidemiol. 2006;59(1):45-52.

7.5. Subgroup analyses

No subgroup analyses are planned. Subgroup analyses, however, might be reported for exploratory purposes.

7.6. Handling of missing data

Imputation of missing data for explanatory variables will be done using Stata's multiple imputation routine with 20 imputations if the total of missing data is below 10%. The variables to impute are the 'Pain is a warning signal to stop physical activity' (yes/no) and the possible confounding variables: age (years, continuous), gender (male/female), and college level education (yes/no). For imputation, we will use a dataset containing all variables in Table1. If there is more than 10% missing data we will exclude non-complete observations. We will not impute the outcome variable.

8. Handling of data

The author responsible for the analysis (AR) will be blinded to the RMDQ score after 52 weeks while cleaning the dataset (baseline data) as well as during imputation of data if this will be performed (7.6). This will be done before collecting the first questionnaire with outcomes. If this is not possible, another author (NR) will be responsible for delivering data without follow-up information. A new dataset only with baseline RMDQ and RMDQ after 52 weeks will be delivered by (NR) to (AR) when follow-up is completed. This to ensure blinding when cleaning and coding this outcome.

9. Ethics

All patients referred to the Spine Center are provided with a standard questionnaire. If patients report having LBP they are then provided with further information about voluntary involvement in a research study and are asked whether they wish to participate. All data is self-reported in questionnaires. Patients may, at any time and without any consequence for their treatment, discontinue participation in the questionnaires. Consenting patients are requested to reply to extra questions in addition to the standard questionnaire and to complete a questionnaire after 52 weeks. Other than filling out and leaving questionnaires, patients will not suffer any harm or inconvenience by participation. The trial is registered with the Danish Data Protection Agency (Central Denmark Region, journal no. 1-16-02-23-17).